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FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 20:02:49 ON 24 JUL 2003

L1 4224 S PTEN
L2 58 S L1 AND GLUCOSE
L3 5 S L1 AND OBESITY
L4 6 S L1 AND OBES?
L5 5 DUP REM L4 (1 DUPLICATE REMOVED)
L6 39 DUP REM L2 (19 DUPLICATES REMOVED)
L7 26 S L6 AND PHOSPHATASE
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L9 0 S PTEN (L) OBESITY (L) GLUCOSE (L) PHOSPHATASE
L10 0 S L2 AND PY<=1997

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L8 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:384548 CAPLUS
DN 133:39116
TI Genes and polypeptides involved in insulin signaling pathways for **glucose** tolerance, obesity, and longevity and their uses as therapeutic and diagnostic tools
SO PCT Int. Appl., 402 pp.
CODEN: PIXXD2
IN Ruvkun, Gary; Ogg, Scott
AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired **glucose** tolerance conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The Caenorhabditis elegans metabolic regulatory genes daf-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositol 3-kinase signaling pathway proteins, resp. Also, the C. elegans PKB kinase and AKT kinase act downstream of these genes, as their mammalian homologs act downstream of insulin signaling. The C. elegans **PTEN** lipid **phosphatase** homolog, DAF-18, acts upstream of AKT in this signaling pathway. Further, the DAF-16 forkhead protein represents the major transcriptional output of this insulin signaling pathway. Addnl. evidence indicates that the DAF-16, DAF-3, DAF-8, and DAF-14 transcriptional outputs of converging signaling pathways regulate metab. The congruence between the C. elegans and mammalian insulin signaling pathways strongly supports the contention that new genes identified in the C. elegans pathway also act in mammalian insulin signaling. Exemplary sequences and functional characteristics of the C. elegans daf genes and their human homologs are provided.

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PI WO 2000033068	A1	20000608	WO 1999-US28529	19991202
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US 2001029617	A1	20011011	US 1998-205658	19981203
EP 1163515	A1	20011219	EP 1999-960641	19991202
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L8 ANSWER 2 OF 26 MEDLINE on STN
AN 2001074377 MEDLINE
TI Regulation of gene expression by **glucose** in pancreatic beta -cells (MIN6) via insulin secretion and activation of phosphatidylinositol 3'-kinase.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Nov 17) 275 (46) 36269-77.
Journal code: 2985121R. ISSN: 0021-9258.
AU da Silva Xavier G; Varadi A; Ainscow E K; Rutter G A
AB Increases in **glucose** concentration control the transcription of the preproinsulin (PPI) gene and several other genes in the pancreatic

islet beta-cell. Although recent data have demonstrated that secreted insulin may regulate the PPI gene (Leibiger, I. B., Leibiger, B., Moede, T., and Berggren, P. O. (1998) Mol. Cell 1, 933-938), the role of insulin in the control of other beta-cell genes is unexplored. To study the importance of insulin secretion in the regulation of the PPI and liver-type pyruvate kinase (L-PK) genes by **glucose**, we have used intranuclear microinjection of promoter-luciferase constructs into MIN6 beta-cells and photon-counting imaging. The activity of each promoter was increased either by 30 (versus 3) mm **glucose** or by 1-20 nm insulin. These effects of insulin were not due to enhanced **glucose** metabolism since culture with the hormone had no impact on the stimulation of increases in intracellular ATP concentration caused by 30 mm **glucose**. Furthermore, the islet-specific glucokinase promoter and cellular glucokinase immunoreactivity were unaffected by 30 mm **glucose** or 20 nm insulin. Inhibition of insulin secretion with the Ca(2+) channel blocker verapamil, the ATP-sensitive K(+) channel opener diazoxide, or the alpha(2)-adrenergic agonist clonidine blocked the effects of **glucose** on L-PK gene transcription. Similarly, 30 mm **glucose** failed to induce the promoter after inhibition of phosphatidylinositol 3'-kinase activity with LY294002 and the expression of dominant negative-acting phosphatidylinositol 3'-kinase (Deltap85) or the phosphoinositide 3'-**phosphatase PTEN** (**phosphatase** and tensin homologue). LY294002 also diminished the activation of the L-PK gene caused by inhibition of 5'-AMP-activated protein kinase with anti-5'-AMP-activated protein kinase alpha2 antibodies. Conversely, stimulation of insulin secretion with 13 mm KCl or 10 microm tolbutamide strongly activated the PPI and L-PK promoters. These data indicate that, in MIN6 beta-cells, stimulation of insulin secretion is important for the activation by **glucose** of L-PK as well as the PPI promoter, but does not cause increases in glucokinase gene expression or **glucose** metabolism.

L8 ANSWER 3 OF 26 MEDLINE on STN
AN 2000400170 MEDLINE
TI Accelerated decline of blood **glucose** after intravenous **glucose** injection in a patient with Cowden disease having a heterozygous germline mutation of the **PTEN**/MMAC1 gene.
SO ANTICANCER RESEARCH, (2000 May-Jun) 20 (3B) 1901-4. Journal code: 8102988. ISSN: 0250-7005.
AU Iida S; Ono A; Sayama K; Hamaguchi T; Fujii H; Nakajima H; Namba M; Hanafusa T; Matsuzawa Y; Moriwaki K
AB The **PTEN**/MMAC1, a putative tumor suppressor, has been demonstrated to dephosphorylate phosphatidylinositol 3, 4, 5-triphosphate, a key molecule involved in the insulin signaling pathway. The **PTEN** may act, therefore, as a negative regulator of insulin signaling. The patient with Cowden disease, having a heterozygous **PTEN**/MMAC1 gene mutation, a C to T substitution of a single base at codon 130, was suspected to have decreased amount of **PTEN** protein with **phosphatase** signature motif. We thought that the patient might be more sensitive to insulin than normal subjects. As expected, administration of a bolus of **glucose** resulted in a more rapid clearance of blood **glucose** than was observed in 5 control subjects, indicating the presence of insulin hypersensitivity in the patient. The euglycemic hyperinsulinemic clamp study provided additional evidence.

L8 ANSWER 4 OF 26 MEDLINE on STN
AN 2000239941 MEDLINE
TI The tumor suppressor **PTEN** negatively regulates insulin signaling in 3T3-L1 adipocytes.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Apr 28) 275 (17) 12889-95. Journal code: 2985121R. ISSN: 0021-9258.
AU Nakashima N; Sharma P M; Imamura T; Bookstein R; Olefsky J M
AB **PTEN** is a tumor suppressor with sequence homology to protein-tyrosine **phosphatases** and the cytoskeleton protein tensin. **PTEN** is capable of dephosphorylating phosphatidylinositol 3,4, 5-trisphosphate in vitro and down-regulating its levels in insulin-stimulated 293 cells. To study the role of **PTEN** in insulin signaling, we overexpressed **PTEN** in 3T3-L1 adipocytes approximately 30-fold above uninfected or control virus (green fluorescent

protein)-infected cells, using an adenovirus gene transfer system. **PTEN** overexpression inhibited insulin-induced 2-deoxy-**glucose** uptake by 36%, GLUT4 translocation by 35%, and membrane ruffling by 50%, all of which are phosphatidylinositol 3-kinase-dependent processes, compared with uninfected cells or cells infected with control virus. Microinjection of an anti-**PTEN** antibody increased basal and insulin stimulated GLUT4 translocation, suggesting that inhibition of endogenous **PTEN** function led to an increase in intracellular phosphatidylinositol 3,4,5-trisphosphate levels, which stimulates GLUT4 translocation. Further, insulin-induced phosphorylation of downstream targets Akt and p70S6 kinase were also inhibited significantly by overexpression of **PTEN**, whereas tyrosine phosphorylation of the insulin receptor and IRS-1 or the phosphorylation of mitogen-activated protein kinase were not affected, suggesting that the Ras/mitogen-activated protein kinase pathway remains fully functional. Thus, we conclude that **PTEN** may regulate phosphatidylinositol 3-kinase-dependent insulin signaling pathways in 3T3-L1 adipocytes.

L8 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:903784 CAPLUS
DN 134:126298
TI Negative regulation of insulin signaling by **PTEN**/MMAC1 in 3T3-L1 adipocytes
SO International Congress Series (2000), 1209, 169-172
CODEN: EXMDA4; ISSN: 0531-5131
AU Nakashima, Naoki; Olefsky, Jerrold M.; Umeda, Fumio; Nawata, Hajime
AB **PTEN** is a tumor suppressor with sequence homol. to protein tyrosine **phosphatases** and the cytoskeletal protein tensin. **PTEN** is capable of dephosphorylating PI(3,4,5)P3 in vitro and down-regulating its levels in insulin-stimulated 293 cells. The authors found that **PTEN** acts as a neg. regulator of insulin signaling pathway in 3T3 L1 adipocytes, and that GLUT4 translocation is actually dependent on the balance between PI3-kinase and **PTEN** activity, although **PTEN**'s physiol. role is still unknown.

L8 ANSWER 9 OF 26 MEDLINE on STN
AN 2001414597 MEDLINE
TI Regulation of phosphoinositide metabolism, Akt phosphorylation, and **glucose** transport by **PTEN** (**phosphatase** and tensin homolog deleted on chromosome 10) in 3T3-L1 adipocytes.
SO MOLECULAR ENDOCRINOLOGY, (2001 Aug) 15 (8) 1411-22.
Journal code: 8801431. ISSN: 0888-8809.
AU Ono H; Katagiri H; Funaki M; Anai M; Inukai K; Fukushima Y; Sakoda H; Ogihara T; Onishi Y; Fujishiro M; Kikuchi M; Oka Y; Asano T
AB To investigate the roles of **PTEN** (**phosphatase** and tensin homolog deleted on chromosome 10) in the regulation of 3-position phosphorylated phosphoinositide metabolism as well as insulin-induced Akt phosphorylation and **glucose** metabolism, wild-type **PTEN** and its **phosphatase**-dead mutant (C124S) with or without an N-terminal myristoylation tag were overexpressed in Sf-9 cells and 3T3-L1 adipocytes using baculovirus and adenovirus systems, respectively. When expressed in Sf-9 cells together with the p110alpha catalytic subunit of phosphoinositide 3-kinase, myristoylated **PTEN** markedly reduced the accumulations of both phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate induced by p110alpha. In contrast, overexpression of the C124S mutants apparently increased these accumulations. In 3T3-L1 adipocytes, insulin-induced accumulations of phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate were markedly suppressed by overexpression of wild-type **PTEN** with the N-terminal myristoylation tag, but not by that without the tag. On the contrary, the C124S mutants of **PTEN** enhanced insulin-induced accumulations of phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate. Interestingly, the phosphorylation level of Akt at Thr308 (Akt2 at Thr309), but not at Ser473 (Akt2 at Ser474), was revealed to correlate well with the accumulation of phosphatidylinositol 3,4,5-trisphosphate modified by overexpression of these **PTEN** proteins. Finally, insulin-induced increases in **glucose** transport activity were significantly inhibited by the overexpression of myristoylated wild-type **PTEN**, but were not enhanced by

expression of the C124S mutant of **PTEN**. Therefore, in conclusion, 1) **PTEN** dephosphorylates both phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate in vivo, and the C124S mutants interrupt endogenous **PTEN** activity in a dominant-negative manner. 2) The membrane targeting process of **PTEN** may be important for exerting its function. 3) Phosphorylations of Thr309 and Ser474 of Akt2 are regulated differently, and the former is regulated very sensitively by the function of **PTEN**. 4) The phosphorylation level of Ser474, but not that of Thr309, in Akt2 correlates well with insulin-stimulated **glucose** transport activity in 3T3-L1 adipocytes. 5) The activity of endogenous **PTEN** may not play a major role in the regulation of **glucose** transport activity in 3T3-L1 adipocytes.

L8 ANSWER 19 OF 26 MEDLINE on STN
AN 2002184354 MEDLINE
TI Specific inhibition of **PTEN** expression reverses hyperglycemia in diabetic mice.
SO DIABETES, (2002 Apr) 51 (4) 1028-34.
Journal code: 0372763. ISSN: 0012-1797.
AU Butler Madeline; McKay Robert A; Popoff Ian J; Gaarde William A; Witchell Donna; Murray Susan F; Dean Nicholas M; Bhanot Sanjay; Monia Brett P
AB Signaling through the phosphatidylinositol 3'-kinase (PI3K) pathway is crucial for metabolic responses to insulin, and defects in PI3K signaling have been demonstrated in type 2 diabetes. **PTEN** (MMAC1) is a lipid/protein **phosphatase** that can negatively regulate the PI3K pathway by dephosphorylating phosphatidylinositol (3,4,5)-triphosphate, but it is unclear whether **PTEN** is physiologically relevant to insulin signaling in vivo. We employed an antisense oligonucleotide (ASO) strategy in an effort to specifically inhibit the expression of **PTEN**. Transfection of cells in culture with ASO targeting **PTEN** reduced **PTEN** mRNA and protein levels and increased insulin-stimulated Akt phosphorylation in alpha-mouse liver-12 (AML12) cells. Systemic administration of **PTEN** ASO once a week in mice suppressed **PTEN** mRNA and protein expression in liver and fat by up to 90 and 75%, respectively, and normalized blood **glucose** concentrations in db/db and ob/ob mice. Inhibition of **PTEN** expression also dramatically reduced insulin concentrations in ob/ob mice, improved the performance of db/db mice during insulin tolerance tests, and increased Akt phosphorylation in liver in response to insulin. These results suggest that **PTEN** plays a significant role in regulating **glucose** metabolism in vivo by negatively regulating insulin signaling.

L8 ANSWER 10 OF 26 MEDLINE on STN
AN 2001173736 MEDLINE
TI Studies of variability in the **PTEN** gene among Danish caucasian patients with Type II diabetes mellitus.
SO DIABETOLOGIA, (2001 Feb) 44 (2) 237-40.
Journal code: 0006777. ISSN: 0012-186X.
AU Hansen L; Jensen J N; Ekstrom C T; Vestergaard H; Hansen T; Pedersen O
AB AIM/HYPOTHESIS: **Phosphatase** and tensin homologue deleted from chromosome ten (**PTEN**) has recently been characterized as a novel member in the expanding network of proteins regulating the intracellular effects of insulin. By dephosphorylation of phosphatidyl-inositol-(3, 4, 5)-trisphosphate (PIP3) the **PTEN** protein regulates the insulin-dependent phosphoinositide 3-kinase (PI3K) signalling cassette and accordingly might function as a regulator of insulin sensitivity in skeletal muscle and adipose tissue. In this study we tested **PTEN** as a candidate gene for insulin resistance and late-onset Type II (non-insulin-dependent) diabetes mellitus in a Danish Caucasian population. METHODS: The nine exons of the **PTEN**, including intronic flanking regions were analysed by PCR-SSCP and heteroduplex analysis in 62 patients with insulin-resistant Type II diabetes. RESULTS: No mutations predicted to influence the expression or biological function of the **PTEN** protein but four intronic polymorphisms were identified: IVS1-96 A-->G (allelic frequency 0.22, 95 % CI: 0.12-0.32), IVS3 + 99 C-->T (0.01, CI: 0-0.03), IVS7-3 TT-->T (0.10, CI: 0.03-0.18) and IVS8 + 32 G-->T (0.35, CI: 0.23-0.47). The IVS8 + 32 G-->T polymorphism was used as a bi-allelic marker for the **PTEN** locus

and examined in 379 patients with Type II diabetes and in 224 control subjects with normal **glucose** tolerance. The IVS8 + 32 G-->T polymorphism in the **PTEN** was not associated with Type II diabetes and it did not have any effect on body-mass index, blood pressure, HOMA insulin resistance index, or concentrations of plasma **glucose**, serum insulin or serum C peptide obtained during an oral **glucose** tolerance test (OGTT). CONCLUSION/INTERPRETATION: Variability in the **PTEN** is not a common cause of Type II diabetes in the Danish Caucasian population.

L8 ANSWER 11 OF 26 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AN 2001:933121 SCISEARCH
TI **PTEN** does not modulate GLUT4 translocation in rat adipose cells under physiological conditions
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (9 NOV 2001) Vol. 288, No. 4, pp. 1011-1017.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
ISSN: 0006-291X.
AU Mosser V A; Li Y H; Quon M J (Reprint)
AB **PTEN** is a 3'-inositol lipid **phosphatase** that dephosphorylates products of PI 3-kinase. Since PI 3-kinase is required for many metabolic actions of insulin, we investigated the role of **PTEN** in insulin-stimulated translocation of GLUT4. In control rat adipose cells, we observed a similar to2-fold increase in cell surface GLUT4 upon maximal insulin stimulation. Overexpression of wild-type **PTEN** abolished this response to insulin. Translocation of GLUT4 in cells overexpressing **PTEN** mutants without lipid **phosphatase** activity was similar to that observed in control cells. Overexpression of **PTEN**-CBR3 (mutant with disrupted membrane association domain) partially impaired translocation of GLUT4. In Cos-7 cells, overexpression of wild-type **PTEN** had no effect on ERK2 phosphorylation in response to acute insulin stimulation. However, Elk-1 phosphorylation in response to chronic insulin treatment was significantly decreased. Thus, when **PTEN** is overexpressed, both its lipid **phosphatase** activity and subcellular localization play a role in antagonizing metabolic actions of insulin that are dependent on PI 3-kinase but independent of MAP kinase. However, because translocation of GLUT4 in cells overexpressing a dominant inhibitory **PTEN** mutant (C124S) was similar to that of control cells, we conclude that endogenous **PTEN** may not modulate, metabolic functions of insulin under normal physiological conditions. (C) 2001 Academic Press.

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L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
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